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HIGH-PRESSURE REACTIONS OF QUINAZOLINE AND INDOLES WITH DIMETHYL ACETYLENEDICARBOXYLATE[1]

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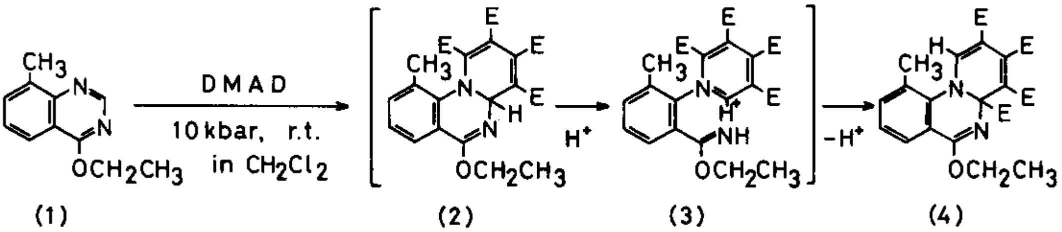
Abstract——4-Ethoxy-8-methylquinazoline, inert at 1 bar, with dimethyl acetylenedicarboxylate at 10 kbar gave tetramethyl 6-ethoxy-10-methyl-4aH-pyrido[1,2-a]quinazoline-2,3,4,4a-tetracarboxylate. 10 kbar pressure gave one new product from this acetylene and indole.

Previously we have reported that 2-bromo-, 2-chloro-, and 2-fluoropyridine, whose nucleophilicities are not high enough for them to attack dimethyl acetylenedicarboxylate (DMAD) at atmospheric pressure, react with the DMAD at 10 kbar at room temperature. 9aH- and 4H-quinolizines are obtained from the bromo- and chloropyridines and a 1:3 adduct from the fluoropyridine.[2] The investigation has now been extended to a quinazoline and two indoles which with DMAD do not react or do so extremely slowly at ambient conditions.

4-Ethoxyquinazoline and its 6-methyl derivative combine with DMAD in refluxing acetonitrile to give 1:2 molar adducts (cf. 2) which undergo rapid rearrangements in the presence of traces of acid to give the isomeric 4aH-pyrido[1,2-a]quinazolines (cf. 4).[3] In contrast, under the same conditions the 8-methyl analogue (1) did not react with DMAD, presumably because of steric hindrance by the methyl group to

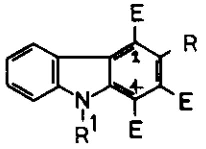


electrophilic attack at nitrogen.[3] The effect of 10 kbar pressure for 1 week at room temperature on a mixture of (1) with DMAD in methylene chloride was examined and gave the rearranged adduct (4)[4] in 34 % yield; m.p. 139-140 °C, ^{1}H-n.m.r. δ ($CDCl_3$) 1.36(t, 3H, J=8 Hz, $-CH_2C\underline{H}_3$), 2.39(s, 3H, 10-$C\underline{H}_3$), 3.55, 3.72, 3.74, 3.96 (each s, 12H, $CO_2C\underline{H}_3$x4), 4.29, 4.36(each q, 2H, J=8 Hz, 18 Hz, $-C\underline{H}_2CH_3$), 7.18-7.68 (ABC pattern, 3H, 7, 8, and 9-H), 7.66(s, 1H, 1-H); ^{13}C-n.m.r. δ($CDCl_3$) 14.1(q, $-OCH_2\underline{C}H_3$), 17.5(q, 10-$\underline{C}H_3$), 51.7, 52.1, 52.6, 53.3(each q, $CO_2\underline{C}H_3$), 62.7(t, $O\underline{C}H_2CH_3$) 75.8(s, 4a-C), 97.0(s, 10-C), 115.2, 123.4, 129.1, 135.4, 136.7(each s, 2,3,4,6a, 10a-C), 122.9, 127.2, 135.2(each d, 7,8, 9-C), 145.8(d, 1-C), 157.6(s, 6-C), 164.1 164.7, 167.8, 168.3(each s, C=O). The rearranged adduct might be formed instead of (2) because of the presence of a trace of acid in the solvent, as for the 4-ethoxyquinazoline adduct.[3] However, stereomodels of (2) and (4) show that there is far less steric compression in the possible intermediate (3) or the rearranged compound (4) so that high pressure might facilitate rearrangement through a concerted [1,5] shift or _via_ (3). It is noteworthy that one sp^2-C resonance of (4) is at much higher field (97.0 δ) than any corresponding atom when the C-methyl group is present at position 6 or is absent from the molecule.[3] This resonance has been assigned to 10-C atom which may have additional sp^3 character because of the steric clash between the attached methyl group and the 1-proton.

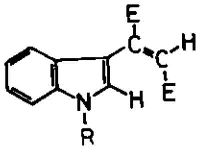
The reaction of indole with DMAD, which proceeds slowly at room temperature, has been carefully investigated[5] and proceeds _via_ charged intermediates formed by initial electrophilic attack by the acetylene at position 3 of the indole. The effect of 10 kbar pressure on this reaction (1:2 moles respectively) in CH_2Cl_2 in a 10 ml capsule at ambient temperature has now been investigated and the results are compared with the earlier observations in Table. Owing to the small scale of the high pressure reactions minor products have doubtless been missed. The most interesting results from the high pressure reactions were the absence of the carbazole (6) under condition B, and the formation of (8), which could be an intermediate leading to (7), under condition C.

1-Methylindole with DMAD under condition B in CH_2Cl_2 gave 20 % of (13) in contrast to 14.5 % of (13) and 4.4 % of (10) obtained in refluxing acetonitrile.[6]

The use of high pressure is clearly valuable where reaction does not occur due to steric hindrance, but for indole the only new feature was the formation of the 1:3 molar adduct (8).



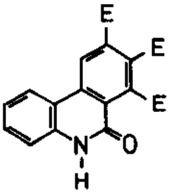
	R	R^1
(5)	H	H
(6)	E	H
(7)	E	E-CE=CHE, 3,4-H_2
(8)	E	Z-CE=CHE, 1,4-H_2



(9) R=H

(10) R=CH_3

E = CO_2CH_3 in all formulae



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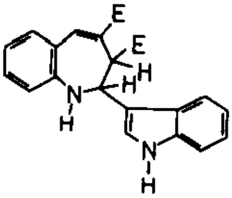

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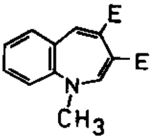

(13)

Table. Products from indole and DMAD at atmospheric pressure (112 days) (A), 10 kbar[7] and either 7days (B) or 1 day (C)

	% Yields		
Product	A*	B	C
Indole (recovered)	18.1	0.6	8.8
(5)	1.0	--	--
(6)	13.4	--	0.8
(7)	7.5	3.7	--
(8)[4,8]	--	--	1.1
(9)[9]	trace	--	0.4
(11)	6.6	--	0.2
(12)	9.8	1.6	--

*From ref.5

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References and Notes

1. Molecular Design Based upon High-Pressure Organic Reactions.I
2. K. Matsumoto, Y. Ikemi, and T. Uchida, J.C.S. Chem. Comm., 543 (1978).
3. P. J. Abbott, R. M. Acheson, M. Y. Kornilov, and J. K. Stubbs, J.C.S. Perkin I, 2322 (1975).
4. Satisfactory elemental analysis and mass spectra data were obtained for this compound, and the ^{1}H and ^{13}C spectra agree with those of other pyrido[1,2-a]-quinazolines.[3]
5. R. M. Acheson, J. N. Bridson, T. R. Cecil, and A. R. Hands, J.C.S. Perkin I, 1569 (1972) and references cited.
6. R. M. Acheson, J. N. Bridson, and T. S. Cameron, ibid., 968 (1972) and references cited.
7. 0.02 mol of the indole and 0.04 mol of DMAD diluted with CH_2Cl_2 was placed in a 10 ml Teflon capsule.
8. m.p. 133-138 °C; ν(KBr) 1740 cm^{-1}; δ($CDCl_3$) 3.52, 3.77(each s, 6H, $OC\underline{H}_3$), 3.72, 3.92(each s, 12H, $OC\underline{H}_3$), 4.45, 5.12(each s, 2H, C-H), 7.25(s, 1H, =C$\underline{H}$), 7.0-7.4, 7.7-7.9, 8.3-8.5(m, 4H).
9. m.p. 113-115 °C; ν(KBr) 1707 cm^{-1}; δ($CDCl_3$) 3.79, 3.95(each s, 3H, $OC\underline{H}_3$), 6.45 (s, 1H, =C$\underline{H}$), 7.2-7.5 and 7.7-7.9(m, 5H), 9.04(br,s, 1H, N$\underline{H}$).

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